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RESPONSE TO OFFICE ACTION

This is in response to the Office Action mailed September 27, 2002 (Paper 6).

Claims 13-24 are pending

Anticipation Rejections

Rejection over Finkenaur

Claims 13-24 were rejected under 35 USC §102(b) as anticipated by Finkenaur *et al.*, EPA 0312208A1 ("Finkenaur"). (Paper No. 6 at 2.) For the reasons set forth below, the rejection, respectfully is traversed.

Finkenaur discloses "[g]el formulations containing polypeptide growth factors having human mitogenic or angiogenic activity are provided. The gel formulations are useful for topical or incisional ***wound*** healing for cutaneous wounds, in the anterior chamber of the eye and other ophthalmic wound healing." (Abstract.)

In making the rejection, the Examiner asserted that:

> "Finkenaur ... discloses the use of a composition comprising a polypeptide growth factor, in particular NGF, in a concentration of 1-500 μg/ml for the treatment of wounds ... [and] teaches that the gels of the invention can be in the form of eye drop formulations or solutions and includes surgically induced ophthalmic wounds, in particular subconjunctival wounds, among the wounds healed by the composition of the invention ...." (Paper No. 6 at 2.)

The Examiner then concluded that:

> "Finkenaur et al. meets the limitation of claims 13-24 ..., as it contemplates methods comprising administering a composition comprising nerve growth factor (NGF) to a subject in need thereof for the treatment of a pathology affecting the internal tissue of the eye."

As is well settled, anticipation requires "identity of invention." *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply,* 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). In a §102(b) rejection there must be no difference between what is claimed and what is disclosed in the applied reference.

In re Kalm, 154 USPQ 10, 12 (CCPA 1967); *Scripps v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

Initially, we note that Finkenaur is discussed at p. 5a of the specification:

> With specific reference to the disorders affecting ***the exposed ocular surface***, i.e. corneal and conjunctival diseases, EP-A-0312208 discloses gel formulations for use in the treatment of epithelial lesions and epithelial pathologies in general, including lesions and pathologies of the ocular surface. The said formulations contain an active ingredient which may be indiscriminately chosen among the various molecules whose name contains the expression "growth factor". Although ***the description is exclusively concerned with the epidermal growth factor (EGF)*** as the preferred active ingredient, and although activity data (*in vitro*) and formulation examples are given only for EGF, other growth factors are mentioned as well, such as FGF (fibroblast growth factor), PDGF (platelet-derived growth factor), TGF-α (transforming growth factor) or the NGF itself. The said growth factors are apparently presented as a family of molecules having equivalent characteristics and biological activity as EGF. As a matter of fact, at the current state of the knowledge, ***it is undisputed that the said growth factors have different specific targets and that they often have conflicting effects, so that they are not considered as biologically equivalent to each other.*** (emphasis added).

The various growth factors mentioned above are different individual molecules, with a different amino acid sequence, structure and molecular weight, and, above all, different receptor sites and different biological activity. For instance, EGF is a 53 amino acid polypeptide having a molecular weight of about 6000 dalton, while NGF is a 140 kdalton molecular complex. Applicant is especially and exclusively claiming a method based on NGF. Finkenaur only incidentally mentioned NGF and does NOT teach the method claimed.

Finkenaur teaches the use of EGF for the treatment of incisional wounds, based on the disclosed mitogenic properties of this compound. (See p. 2, lines 17-24). Finkenaur discloses the direct application of the product on a wound, whether it be a surface wound or an internal wound. (See p. 4, lines 7-13). Finkenaur is directed towards applying the product to the damaged

site/wound as opposed to the claimed invention, which is based on the unexpected finding that NGF is able to ***pass through the ocular tissues***, so that, in order to treat internal ocular tissues, the product need only be applied onto the ocular surface, *i.e.*, it does not need to be directly applied onto the affected site (wound).

The Examiner states that Finkenaur "contemplates" the presently claimed method by administering NGF to treat a pathology affecting the internal tissue of an eye. (Paper No. 6 at 2.) The presently claimed method, however, recites that the treatment occurs by administering "onto the ocular surface." Thus, the rejection does not – and cannot – identify where in Finkenaur it is disclosed to administer "onto the ocular surface." Thus the rejection is factually and legally deficient and should be withdrawn.

Rejection over Louis

Claims 13-20 were rejected under 35 USC §102(e) as anticipated by Louis *et al.*, U.S. Patent Application 5,736,516 ("Louis"). (Paper No. 6 at 3.) Applicant respectfully traverses this rejection. The Examiner asserted that:

> "Louis provides a method for treating vision loss due to photoreceptor degeneration, comprising the intraocular administration of glial cell-derived neurothropic factor (GDNF) in a dose of .001 – 10 mg/day (See col. 4, line 50 to col. 5, line 17). Louis teaches that the GDNF includes natural, synthetic or recombinant GDNF and comprises the GDNF's, which are homologous to the human GDNF (See col. 7, lines 36-45.) Louis contemplates pharmaceutical compositions comprising delivery vehicles, including ophthalmic solutions, suspensions and ointments, and formulations for subconjuctival, orbital and intracameral injection (See col. 16, line 45 to col. 18, line 49). Louis teaches that additional formulations may include materials, which provide for prolonged ocular residence, such as polymers and gel-forming materials (See col. 19, lines 51-65)."

The Examiner then concluded that Louis's method meets the limitations of claims 13-20 because it contemplates methods comprising administering a composition comprising nerve

growth factor (NGF) to a subject in need thereof for the treatment of a pathology affecting the internal tissue of an eye," and, therefore, anticipates the claimed invention.

As noted above anticipation requires "identity of invention." In a §102 rejection there must be no difference between what is claimed and what is disclosed in the applied reference. *In re Kalm*, 154 USPQ 10, 12 (CCPA 1967); *Scripps v. Genentech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). However, Louis does not recite all the elements of the claimed invention. In particular, Louis does not disclose the use of nerve growth factor (NGF). Louis is concerned with the treatment of retinal affections, and diseases affecting the optic nerve, based on the use of another "growth factor:" GDNF, i.e. Glial cell line-Derived Neurotrophic Factor. GDNF is a biologically active agent very different from NGF, having no features in common therewith but the fact that they both belong to the large family of neurotrophic factors. However, while NGF more properly belongs to the family of neurotrophins (see from col. 1, line 58 to col. 2, line 6), GDNF belongs to the family of neurokines, and is more similar in structure to TGF-β (see col. 2, lines 19-28).

The GDNF family is characterized by the binding to a specific receptor, RET, completely different (in terms of structure, mechanism of function and activity) from the p75 and Trk receptors that bind the neurotrophin family. Moreover, NGF and GDNF show completely different structures that justify both their binding to different receptors and their different biological action. For example, GDNF exerts a potent neurotrophic effect on dopaminergic neurons both *in vitro* and *in vivo* (see, e.g., Lin L.F.H. et al., Science 260:1130-2, 1993, cited in Yan *et al.* U.S. Patent

No. 5,641,749), while NGF does not act on these neurons (Granholm A.C. et al., Exp. Brain Res. 116:29-38, 1997). 1/

In view of the foregoing, it is clear that GDNF disclosed by Louis as being useful in treating retinal affections and diseases affecting the optic nerve is clearly not the same as the claimed method of administering NGF "onto the ocular surface." Thus the rejection is factually and legally deficient, and it is respectfully requested that it be reconsidered and withdrawn.

Rejection over Okamoto

Claims 13-20 were rejected under 35 U.S.C. § 102(a) as being anticipated by Okamoto, WO 98/10785 ("Okamoto"). (Paper No. 6 at 4.) Okamoto[2/] discloses "remedies for optic nerve function disorders ...; and contact lenses containing these remedies." In making the rejection, the Examiner asserted that "[the] patent provides an ophthalmic composition for subconjunctival and ocular injection to treat optic nerve disorders, said composition comprising NGF in an amount of 10^{-3} to 2 x 10^5 μg/ml (See pp. 3-4)."

The Examiner then concluded that "[t]he method disclosed by the patent meets the limitations of claims 13-20 ... as it contemplates methods comprising administering a composition comprising nerve growth factor (NGF) to a subject in need thereof for the treatment of a pathology affecting the internal tissue of an eye."

The concentration of the active ingredient in Okamoto's composition is not, as the Examiner states, 10^{-3} to 2 x 10^5 **μg/ml**, but rather 10^{-3} to 2 x 10^5 **μg/l**. The actual disclosed range of 10^{-3} to 2 x 10^5 **μg/l** (See pp. 3-4) is much broader than applicant's claimed range of 10 to 500 **μg/ml**. The MPEP § 2131.03 makes clear that for a range to be anticipated by the prior art, the

1/ These references are presently unavailable to applicant's attorneys. If the Examiner wishes to obtain copies, please contact the undersigned who will ensure that they are made available.

prior art must disclose a range within, overlapping, or touching the claimed range so that the prior art range discloses the claimed range with "sufficient specificity." (See MPEP § 2131.03 at 2100-72). The MPEP § 2131.03 further states:

> When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. The unexpected results may also render the claims unobvious. The question of "sufficient specificity" is similar to that of "clearly envisaging" a species from a generic teaching. See MPEP § 2131.02 . A 35 U.S.C. 102/103 combination rejection is permitted if it is unclear if the reference teaches the range with "sufficient specificity." The examiner must, in this case, provide reasons for anticipation as well as a motivational statement regarding obviousness. Ex parte Lee 31 USPQ2d 1105 (Bd. Pat. App. & Inter. 1993) (expanded Board). For a discussion of the obviousness of ranges see MPEP § 2144.05 . (Id.)

The range disclosed by Okamoto - 10^{-3} to 2 x 10^5 **μg/l** - is not ***a range which touches, overlaps or is within the claimed range***. This requires withdrawal of the rejection. Even if the reference had disclosed a range which touched, overlapped or was within the claimed range, ***no specific examples falling within the claimed range are disclosed.*** The only actual data available, given in the examples, recite NGF concentrations, in an ophthalmic solution, of **0.04 and 0.02 μg/ml**, each of which is well outside the claimed range. Therefore, in order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." As explained above, what constitutes a "sufficient

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2/ Applicant notes that the reference is in Japanese. Applicant's attorneys do not have an English translation. If the Examiner has access to an English translation of Okamoto, she is asked to provide it to the undersigned.

specificity" is fact dependent. Here, the Examiner has not provided any analysis why the disclosed range of 10^{-3} to 2 x 10^{5} **µg/l** would anticipate a claimed range of 10 to 500 **µg/ml.** The absence of such an analysis also requires withdrawal of the rejection.

In this case, the range disclosed by Okamoto is enormously broader than the claimed range. Specifically, Okamoto's disclosed range covers about 8 orders of magnitude, while the claimed range is only about 2 orders of magnitude. The claimed range may be thought of as a "species" to the broad "genus" disclosed by Okamoto. Certainly nothing in Okamoto's disclosure would have allowed one of ordinary skill in the art to envision the narrow range recited in applicant's claims.

Finally, applicant wishes to point out that experiments were run, using the methods described in his specification, which showed that concentrations of NGF employed by Okamoto in his examples (0.02 and 0.04 µg/ml) are at least 25 times lower than the lowest concentrations needed to show any trace of NGF passing through the cornea and taken into the internal occular tissues. This data can be formally presented to the Examiner, if she would deem it helpful.

For the reasons presented above, this anticipation rejection with regard to claims 13-20 over Okamoto should be withdrawn.

Obviousness Rejections

Rejection of Finkenaur

Claims 13-24 were rejected under 35 USC §103(a) as being unpatentable over Finkenaur. (Paper No. 6 at 4.) In making the rejection, the Examiner asserted that:

> "[i]t would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Finkenaur et al. to device methods for the treatment of pathologies affecting the internal tissue of the eye, comprising administering NGF in the amount disclosed in the publication. The expected result would have been successful methods of treatment of the pathology in the eye." (Paper No. 6 at 4.)

The Examiner then concluded that:

> "[b]ecause of the teachings of Finkenaur et al., that NGF is effective in treating ophthalmic wounds, including internal wounds, one of ordinary skill in the art would have a reasonable expectation of success that the methods claimed in the instant application would be successful. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made." (*Id.* at 5.)

The Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152. It is axiomatic that an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would ***impel*** one skilled in the art ***to do what the patent applicant has done.*** *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993).

Here, as explained above with regard to the Examiner's anticipation rejection, Finkenaur clearly distinguishes its process from the presently claimed method. The various growth factors mentioned in Finkenaur are different individual molecules, with a different amino acid sequence, structure and molecular weight, and, above all, different receptor sites and different biological activity. Applicant is claiming a method based on NGF. Finkenaur only incidentally mentioned NGF, and does not teach or suggest the presently claimed method.

Finkenaur teaches the use of EGF for the treatment of incisional wounds, based on the disclosed mitogenic properties of this compound. (See p. 2, lines 17-24). Finkenaur discloses the direct application of the product on a wound, whether it be a surface wound or an internal wound. (See p. 4, lines 7-13). The Examiner's conclusion that "[b]ecause of the teachings of Finkenaur et al., that NGF is effective in treating ophthalmic wounds, including internal wounds, one of ordinary skill in the art would have a reasonable expectation of success that the methods

claimed in the instant application would be successful" is in error. (Paper No. 6 at 4-5.) The method as claimed is for treatment by administering onto the ocular surface. Finkenaur, however, is concerned with direct application of the product on the wound. Finkenaur does not teach or suggest applicant's unexpected finding that NGF is able to pass through the ocular tissues, so that the product need only be applied to the ocular surface, not directly to the affected area or wound. Thus the rejection is factually and legally deficient and should be withdrawn.

Rejection over Hammang

Claims 13-24 were rejected under 35 USC §103(a) as being unpatentable over Hammang et al., U.S. Patent 6,436,427. (Paper No. 6 at 5.) Hammang discloses a "method for delivering biologically active molecules to the eye by implanting biocompatible capsules containing a cellular source of the biologically active molecule. Also provided is a method of treating ophthalmic diseases using biocompatible capsules." (Abstract).

In making the rejection, the Examiner asserted that Hammang:

> "discloses the intraocular delivery of neurothropic factors, including NGF, in the dosage range of 50-500 ng, for the treatment of ophthalmic diseases, including retinal vascular diseases, choroidal disorders and tumors, vitreous disorders, trauma, post-cataract complications and optic neuropathies (See col. 5, line 1 to col. 6, line 7 and col. 10, lines 32-46). Hammang et al. contemplates implanting living cells comprising the active agent into the vitreous of the eye (See col. 11, lines 7-24)." (Paper No. 6 at 4.)

The Examiner acknowledged, however, that "Hammang does not provide the amount of the active agent in μg/ml ...." (*Id.*) To fill this gap, the Examiner stated that "one of ordinary skill in the art would have been able to determine the final concentration of the active agent by routine experimentation." (*Id.*)

The Examiner then concluded that

> "it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Hammang et al. to

> devi[s]e methods for the treatment of pathologies affecting the internal tissue of an eye, comprising administering NGF, as disclosed in the patent. The expected result would have been successful methods of treatment of the pathology in the eye. Because of the teachings of Hammang et al., that NGF is effective in treating ophthalmic diseases, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful." (Paper No. 6 at 5-6.)

Initially, as acknowledged by the Examiner, Hammang does not provide the amount of the active agent in μg/ml. The Examiner then states that one would have been able to find the final concentration by "routine experimentation." (Paper No. 6 at 5). The Examiner has provided no guidance as to ***why*** one of ordinary skill in the art would have been able to determine the final concentration. The Examiner has failed to point to any reasoning in the reference or elsewhere that would lead one to the concentration as claimed. An Examiner's belief or conjecture is no substitute for statutory prior art. *In re Kratz*, 201 USPQ 71, 76 (CCPA 1979) *citing*, *In re Antonie*, 195 USPQ 6 (CCPA 1977). ("We have previously rejected the argument that undirected skill of one in the pertinent art is an adequate substitute for statutory prior art."). However, unsupported conjecture as to what one of ordinary skill in the art would do by "***routine experimentation***" is all that the rejection offers. Simply put, that is not enough to support a *prima facie* case of obviousness. The rejection has substituted conjecture as to what one skilled in the art would believe for the required statutory reference. For this additional reason the rejection of claims 13-24 should be withdrawn.

In addition, Hammang discloses the intraocular delivery of an active ingredient by means of a surgically implanted device, i.e., a capsule. This is entirely different than the claimed method, where NGF has been found to be able to penetrate through ocular tissues upon administration onto the external surface of the eye. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02.

Therefore, the Examiner's reasoning is inconsistent with the actual disclosure of the reference. The reference is void of any disclosure ***why*** one of ordinary skill would deviate from "implanting biocompatible capsules" and arrive at the claimed method of administering onto the external surface of the eye. There must be some suggestion or motivation, either in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference before one of ordinary skill could have a reasonable expectation of success. See MPEP § 2142.

For the reasons presented above, the obviousness rejection with regard to claims 13 - 24 should be withdrawn.

Rejection over Reich

Claims 13-24 were rejected under 35 USC §103(a) as being unpatentable over Reich, U.S. Patent 4,973,466 in view of Finkenaur. (Paper No. 6 at 6.) The Examiner asserted that:

> "Reich discloses a method for healing surgical and natural wounds in eye tissues, including sclera (See col. 1, lines 5-18). Reich teaches that the compositions of the invention can be formed into sheets or strips and comprise a gel and a medicament, including NGF (See col. 2, line 60 to col. 6, line 29). Thus, Reich provides a method for treating a pathology affecting the internal tissue of an eye." (*Id.*)

The Examiner acknowledged, however, that "Reich is deficient in the fact, that it does not disclose the amount of NGF used in the invention." (*Id.*) To fill the gap, the Examiner stated that "Finkenaur et al. discloses the use of a composition comprising a polypeptide growth factor, in particular NGF, in a concentration of 1-500 μg/ml for the treatment of ophthalmic wounds (See p. 4, lines 7-13)." (*Id.*)

The Examiner then concluded that:

> "it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Reich and

> Finkenaur et al., to device methods for the treatment of pathologies affecting the internal tissue of an eye, comprising administering NGF, as disclosed in the prior art. The expected result would have been successful methods of treatment of the pathology in the eye. Because of the teachings of Reich and Finkenaur et al., that NGF is effective in treating ophthalmic diseases, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant invention would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made." (*Id.*)

Applicant respectfully submits that the rejection uses the wrong standard for determining obviousness. The rejection states "[b]ecause of the teachings of Reich and Finkenaur ... NGF is effective in treating ophthalmic diseases, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant invention would be successful." The Examiner has not indicated ***why*** one of ordinary skill in the art would have had a reasonable expectation of success of the claimed method. In addition, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would ***impel*** one skilled in the art to do what the patent applicant has done. *Ex parte Levengood*, 28 USPQ2d at 1301-02.

Even if Reich and Finkenaur were combined in the manner suggested by the Examiner (and applicant submits that there would have been no reason to do so), the proposed combination does not disclose or suggest the process recited in the claims. Reich discloses a method for preparing wound healing dressings. (See col. 1, lines 5-18). The disclosure in Reich, as does Finkenaur, concerns medicaments to be applied onto the surface of the affected area, *i.e.*, the surgical or natural wound sustained to the tissue of the eye. (*Id.*) Finkenaur teaches the use of EGF for the treatment of incisional wounds, based on the disclosed mitogenic properties of this compound. (See p. 2, lines 17-24). Finkenaur discloses the direct application of the product on a wound, whether it be a surface wound or an internal wound. (See p. 4, lines 7-13). It is clear that Reich and Finkenaur concern applying the product to the damaged site/wound as opposed to the

claimed invention, which is entirely based on the unexpected finding that NGF is able to ***pass through the ocular tissues***, so that, in order to treat internal ocular tissues, the product need only be applied onto the ocular surface, *i.e.*, it does not need to be directly applied onto the affected site (wound).

Neither Reich nor Finkenaur teach or suggest administering an active agent to the ocular surface as claimed. The Examiner has failed to address this distinction and to provide any reason why one would ignore the express disclosure of the documents. For this reason alone, the rejection should be withdrawn.

For the reasons set forth above, withdrawal of all rejections, and allowance of the claims is respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on March 27, 2003.

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